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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,005	GRIFFIN ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/7/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 13-30 are pending.

Election/Restriction

2. Applicant's election with traverse of Group I, Claims 13-30 in a paper dated 10/04/2004 is acknowledged. Applicants argue: "[t]he claims to be modified to conform to the present restriction requirement, it would mean redefining the invention in a manner conceived of not by the inventors but by the Examiner. This course would lead to the dilemma forseen in *In re Weber* where the invention as defined by the Examiner is not necessarily described in the specification. Clearly forming sub-genuses of compounds based on USPTO search classification schemes of certain substituents, does not necessarily correspond to the subgenus determined by the inventors from their research. A restriction practice in which the genus of compounds that is allowed to be claimed is defined *ex post facto* by the Examiner leaves the Applicants incapable of drafting a specification with proper antecedent basis for the claims that ultimately result from the examination process."

The examiner disagrees with applicant's argument. The inventors as presented in the specification define the invention. Drafting of specification is done first at the time of filing an application, thus, the "drafting" of the specification does not depend on the Examiner's restriction requirement. The examiner did not create a restriction requirement that would create lack of antecedent basis for the claims. Applicants claim a compound of formula L-X-L and the restriction was made based on the L (ligand moiety) that is always present in the claims. Each group is based on L choices clearly

set forth, so no description problem can arise. Note that the same restriction was made in the parent.

In regard to the argument that "sub-genuses of compounds based on USPTO search classification schemes of certain substituents, does not necessarily correspond to the subgenus determined by the inventors from their research", the examiner disagrees with this argument. Applicant's election of Group I (L = formulae XI, XII, XIII) would include the sub-genus of Groups II-XII and the linkers as claimed. Applicants are entitled to join various moieties as long as the classification of the other moiety is not higher than the elected invention. Since applicants elected Group I (L = unfused pyrimidine), applicants are entitled to have other moieties examined along with Group I. Specifically, Group I – linker - Group II, Group I – linker – Group III, Group I – linker – Group IV ....Group I – linker – Group XII. Note that Group I is always present in left hand side and another moieties selected from Group II-Group XII is permitted on the right hand side.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of many of the diseases recited in claim 30, does not reasonably provide enablement for the treatment of neoplasia, chronic inflammatory disease and arthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There has been recited a method of treating neoplasia, chronic inflammatory disease and arthritis, but the specification is not enabled for such a scope.

Neoplasia - literally "new growth", refers to abnormal cell growth which may form benign or malignant tumors (cancer). The claim sets forth the treatment of cancer or malignant tumors generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a “silver bullet” is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and

different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Enablement for the scope of "chronic inflammatory disease" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, chronic inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper

lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus.

Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space.

Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-18 and IL-18, and IFN-.

Other inflammations in the respiratory system include CF, adult respiratory distress syndrome, asthma and bronchitis.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at

stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis").

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

Prostatitis, inflammation of the prostate, comes in several different forms, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

It has been recited a treatment of arthritis in general, but the specification is not enabled for such a scope. Arthritis is very broad and it includes among others osteoarthritis, rheumatoid arthritis and gouty arthritis. These operate via very different mechanisms. For example, gouty arthritis arises from an overproduction of uric acid, or a reduced ability of the kidney to eliminate uric acid so that uric acid sodium salt builds up in joints. Osteoarthritis is characterized by the breakdown of the joint's cartilage. Cartilage

breakdown causes bones to rub against each other, causing pain and loss of movement. Rheumatoid arthritis is a chronic inflammatory illness. It is an autoimmune disease in which the immune system attacks normal tissue components as if they were invading pathogens. Since the nature of arthritis is very broad and the diseases such as osteoarthritis, rheumatoid arthritis and gouty arthritis operate in different mechanism, the enablement rejection is proper.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 13 and claims dependent thereon are rejected because the term "substituted" is indefinite. In the absence of the specific moieties intended to effectuate modification by the "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein applicants fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicants regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

b. In claim 13 or elsewhere in the claims, the term "heterocyclic" is indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf *In re Wiggins*, 179 USPQ 421, 423.

c. In claim 13 or elsewhere in the claims, the term "oxyacylamino" is not clear. What is it? Is this a divalent or a monovalent? How is it attached to the ring? Is it attached to the ring thru nitrogen i.e. –NH-acyloxy or is it attached thru the oxygen i.e. -O-acylamino? Or both e.g. –O-Acyl-N- ?

d. In claim 13 or elsewhere in the claims, the term "acyl" is indefinite. Does this embrace acids of S? P? As? What does the stem look like, i.e. if the acyl is e.g. RC(O), what is R?

e. In claim 13, the term "heteroaryl" and "heterocyclic" are recited for the substituent choices for R, R', and R" (on the last paragraph on claim 1). "Heterocyclic" is broader term, thus "heteroaryl" seems redundant. It is recommended that applicants delete the term "heteroaryl". Like wise, the same terms are recited on page 5 for the definition of the variable R_{aa}.

f. In claim 17, the term "analogs" is indefinite. Analogs to what? What are included by the said phrase and what are not?

g. In claim 29, there has been recited a method of treating a disease or medical disorder mediated by a protein kinase. The scope of claim 29 is unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such mediator will surely involve undue experimentation. Suppose that a given inhibitor "compound X" when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many

different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

G. It is also not clear which kinases are intended, since there are dozens of known protein kinases. Thus, it must be repeated with each known protein kinases.

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571) 272-0674, if there is no reply within 24 hours, James Wilson (Acting SPE) can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

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KH
October 25, 2004